Novel Synthon of *N*-Boc-Phytosphingosine-3,4-thiocarbonate for the Synthesis of Sphingosine Derivatives

Bo Gan Song, Bum Suk Son, Min Jung Seo, Jung Ki Kim, Gehyeong Lee, Zaesung No, and Hyoung Rae Kim*

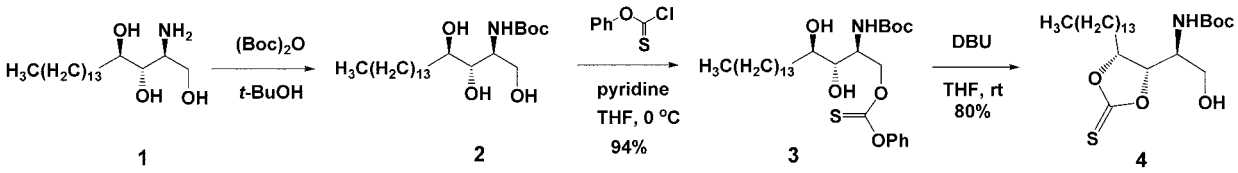
Medicinal Science Division, Korea Research Institute of Chemical Technology, P. O. Box 107, Yusong, Daejeon 305-600, Korea
**E-mail: hyungrk@krict.re.kr*
Received November 27, 2004

Key Words : Sphingosine, *N*-Boc-Phytosphingosine-3,4-thiocarbonate, 3-Dehydroxy-phytosphingosine, 2-Amino-octadec-3-en-1-ol

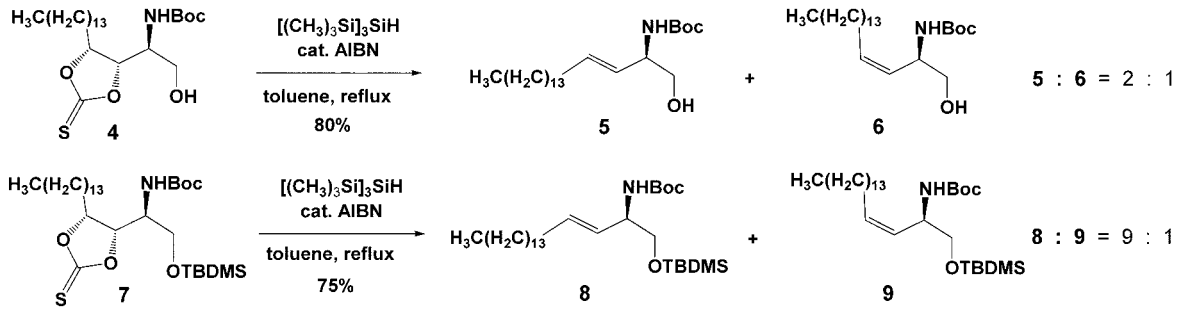
Phytosphingosine, one of the major sphingosine derivatives was found in microorganisms, yeast, plants, and fungi as a major membrane component, and also found in many mammalian tissues[1] and interestingly in some cancer cell-types.[2] The roles of sphingosine derivatives have been enigmatic but they are recently proved to be essential in cell communications and regulation of cell growth.[3] Sphingosine-1-phosphate, the most focused compound in sphingosine derivatives is known to affect fundamental cellular functions,[4] it can also reduce mortality in hypoxic cardiac myocytes,[5] and proved to be crucial in cancer development and progression.[6] Much attention has also been paid to KRN7000, one of α-galactosylceramides as an interesting immunomodulator, which will be useful for treatment of immune related diseases.[7] Since the sphingosine derivatives are very interesting both biologically and synthetically, recently many attempts have been tried to synthesize not only natural sphingosine derivatives[8] but also new modifications of sphingosine derivatives for the evaluation of biological activities.[9]

Previously, we reported a novel synthesis of *N*-Boc-phytosphingosine-3,4-carbonate as an intermediate for the synthesis of new phytosphingosine derivatives, however we could only modify 1-position of phytosphingosine from the intermediate.[10] Here we wish to report a new synton for the synthesis of various sphingosine derivatives. *N*-Boc-Phytosphingosine (**2**)[10] was reacted with phenyl chlorothionocarbonate and pyridine at 0 °C in THF to afford **3** in good yield. To the reaction mixture was added 1.2 equiv of DBU at 25 °C, the thiocarbonate at 1-position was migrated to 3-position, and then the cyclic thiocarbonate **4** was formed as sticky solid in 65% yield as shown in Scheme 1.[11]

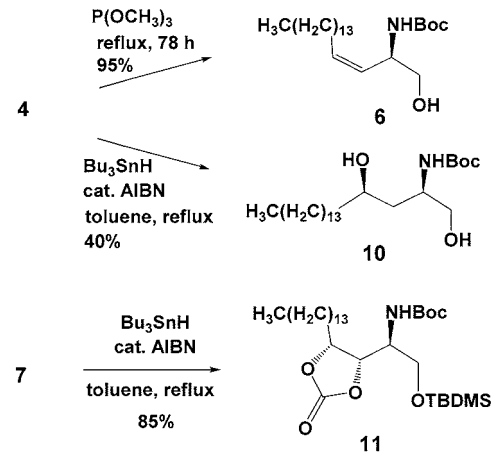
Hydrolysis of **4** with potassium carbonate in 95% methanol afforded *N*-Boc-phytosphingosine (**2**) quantitatively. For the reductive elimination of **4**, first we examined tributyltin hydride or triphenyltin hydride in the presence of triethylborane, but the reaction did not occur at all. When **4** was heated in toluene with tri(trimethylsilyl)silane in the presence of *cat.* AIBN, the thiocarbonate group in **4** was reduced to the double bond to form **5** and **6**[12] in a ratio of 2 : 1 in total 80% yields, while after protection of hydroxyl group of **4** with TBDMS, the *trans* double bond (**8**) was formed as a major in a ratio of 9 : 1 as shown in Scheme 2. The aminoalcohols, **5** and **6** showed potent biological



Scheme 1



Scheme 2



Scheme 3

activities[13] and these compounds could be easily converted to other sphingosine derivatives.[14]

When **4** was heated in trimethyl phosphite for 78 h, only *cis* double bond was formed to give **6** in 95% yield as shown in Scheme 3. Interestingly, when tributyltin hydride was used with AIBN, **10** was separated in 40% yield from a complicated mixture. **5** and **6** were not formed in the reaction but any other compounds could not be isolated. The structure of **10**[15] was confirmed by COSY and NOE experiment. Moreover, **7** afforded only desulfurized product **11**, the spectral data of which were in accordance with those previously reported.[10]

In summary, phytosphingosine was protected by the formation of novel cyclic thiocarbonate in two steps, which could be useful for the derivatization of phytosphingosine by reductive cleavage of the thiocarbonate ring.

Acknowledgement. This research was supported financially by the Ministry of Science and Technology in Korea.

References and Notes

1. (a) Karlsson, K. A. *Acta Chem. Scand.* **1964**, *18*, 2295. (b) *ibid*. **1964**, *18*, 2297. (c) Karlsson, K. A.; Samuelsson, B. E.; Steen, G. O. *Acta Chem. Scand.* **1968**, *22*, 1361. (d) Wertz, P. W.; Miethke, M. C.; Long, S. A.; Stauss, J. S.; Downing, D. T. *J. Invest. Dermatol*. **1985**, *84*, 410. (e) Schmidt, R. P. In *Liposome Dermatics*; Braun-Falco, O. H.; Corting, C.; Maibach, H. I. Eds.; Springer-Verlag: Berlin, Heidelberg, 1992; pp 44-56. (f) Barenholz, Y.; Gatt, S. *Biochem. Biophys. Res. Commun*. **1967**, *27*, 319. (g) Takamatsu, K.; Mikami, M.; Kikuchi, K.; Nozawa, S.; Iwamori, M. *Biochim. Biophys. Acta* **1992**, *1165*, 177. (h) Okabe, K.; Keenan, R. W.; Schmidt, G. *Biochem. Biophys. Res. Commun*. **1968**, *31*, 137. (i) Vance, D. E.; Sweeley, C. C. *J. Lipid Res*. **1967**, *8*, 621.
2. Kanfer, J. N.; Hakomori, S. In *Handbook of Lipid Research, Vol. 3, Sphingolipid Biochemistry*; Hanahan, D., Ed.; Plenum Press: New York, 1983.
3. (a) Lee, Y. J.; Hannun, Y. A.; Obeid, L. M. *J. Biol. Chem*. **1996**, *271*, 13169. (b) Hannun, Y. A. *J. Biol. Chem*. **1994**, *269*, 3125. (c) Gomez-Munoz, A.; Waggoner, D. W.; O'Brien, L.; Brindley, D. N. *J. Biol. Chem*. **1995**, *270*, 26318. (d) Merill Jr., A. H. *Nutr. Rev.* **1992**, *50*, 78. (e) Merill Jr., A. H.; Schmelz, E.-M.; Dillehsy, D. L.; Spiegel, S.; Shayman, J. A.; Schroeder, J. J.; Riley, R. T.; Voss, K. A.; Wang, E. *Toxicol. Appl. Pharmacol*. **1997**, *142*, 208. (f) Merill Jr., A. H. *J. Bioenerg. Biomembr.* **1991**, *23*, 83.
4. (a) Ishii, I.; Fukushima, N.; Ye, X.; Chun, J. *Annual Review of Biochemistry* **2004**, *73*, 321. (b) Anlinker, B.; Chun, J.; Helen, L. D. *Journal of Biological Chemistry* **2004**, *279*, 20555.
5. Karliner, J. S. *Journal of Cellular Biochemistry* **2004**, *92*, 1095.
6. Ogretman, B.; Hannun, Y. A. *Nature Reviews Cancer* **2004**, *4*, 604.
7. (a) Morita, M.; Motoki, K.; Akimoto, K.; Natori, T.; Sakai, T.; Sawa, E.; Yamaji, K.; Koezuka, Y.; Kobayashi, E.; Fukushima, H. *J. Med. Chem.* **1995**, *38*, 2176. (b) Shimosaka, A. *Int. J. Hematol.* **2002**, *76*, 277.
8. (a) Koskinen, P. M.; Koskinen, A. M. P. *Synthesis* **1998**, 1075. (b) He, L.; Byun, H.-S.; Bitterman, R. *J. Org. Chem*. **2000**, *65*, 7618. (c) Chun, J.; He, L.; Byun, H.-S.; Bitterman, R. *J. Org. Chem*. **2000**, *65*, 7634. (d) Jo, S. Y.; Kim, H. C.; Jeon, D. J.; Kim, H. R. *Heterocycles* **2001**, *55*, 1127. (e) Olofsson, B.; Somfai, P. *J. Org. Chem.* **2003**, *68*, 2514. (f) Raghavan, S.; Rajender, A. *J. Org. Chem.* **2003**, *68*, 7094. (g) van den Berg, R. J. B. H. N.; Korevaar, C. G. N.; Overkleeft, H. S.; van der Marel, G. A.; van Boom J. H. *J. Org. Chem*. **2004**, *69*, 5699. (h) Kim, S.; Song, S.; Lee, T.; Jung, S.; Kim, D. *Synthesis* **2004**, *6*, 847.
9. (a) Clemens, J. J.; Davis, M. D.; Lynch, K. R.; MacDonald, T. L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3401. (b) Dagan, A.; Wang, C.; Fibach, E.; Gatt, S. *Biochim. Biophy. Acta* **2003**, *1633*, 161. (c) Lim, H.-S.; Oh, Y.-S.; Suh, P.-G.; Chung, S.-K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 237. (d) Sun, C.; Bitterman, R. *J. Org. Chem*. **2004**, *69*, 7694. (e) Clemens, J. J.; Davis, M. D.; Lynch, K. R.; MacDonald, T. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4903. (f) Goff, R. D.; Gao, Y.; Mattner, J.; Zhou, D.; Yin, N.; Cantu, III, C.; Teyton, L.; Bendelac, A.; Savage, P. B. *J. Am. Chem. Soc.* **2004**, *126*, 13602. (g) Lu, X.; Byun, H.-S.; Bitterman, R. *J. Org. Chem*. **2004**, *69*, 5433.
10. Jo, S. Y.; Kim, H. C.; Woo, S. W.; Seo, M. J.; Lee, G.; Kim, H. R. *Bull. Korean Chem. Soc.* **2003**, *24*(3), 267.
11. **3**: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.9 Hz), 1.24-1.53 (m, 24H), 1.47 (s, 9H), 1.53-1.63 (m, 2H), 2.14 (br, 1H, -OH), 2.90 (br, 1H, -OH), 3.66-3.75 (m, 2H), 4.12-4.18 (m, 1H), 4.70-4.85 (m, 2H), 5.10 (d, 1H, J = 6.2 Hz, -NH), 7.08-7.45 (m, 5H). **4**: ^{1}H NMR ($CDCl_3$) δ0.88 (t, 3H, J = 6.2 Hz), 1.24-1.48 (m, 24H), 1.45 (s, 9H), 1.76-1.82 (m, 2H), 1.85 (br, 1H, -OH), 3.75-3.81 (m, 1H), 3.93-4.10 (m, 2H), 4.86-4.95 (m, 2H), 5.02 (br, 1H, -NH).
12. **5**: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.4 Hz), 1.20-1.45 (m, 24H), 1.45 (s, 9H), 1.94-2.05 (m, 2H), 2.25 (br, 1H, -OH), 3.50-3.72 (m, 2H), 4.10-4.22 (m, 1H), 4.78 (br, 1H, -NH), 5.36 (dd, 1H, J = 6.1, 15. 4Hz), 5.62-5.78 (m, 1H); Anal. calcd for $C_{23}H_{45}NO_3$: C, 72.01; H, 11.82; N, 3.65; O, 12.51. Found: C, 72.051; H, 11.918; N, 3.646. **6**: ^{1}H NMR ($CDCl_3$) δ0.88 (t, 3H, J = 6.5 Hz), 1.18-1.40 (m, 24H), 1.45 (s, 9H), 2.05-2.225 (m, 2H), 2.50 (br, 1H, -OH), 3.50-3.65 (m, 2H), 4.40-4.56 (m, 1H), 4.62 (br, 1H, -NH), 5.18-5.35 (m, 1H), 5.50-5.68 (m, 1H); Anal. calcd for $C_{23}H_{45}NO_3$: C, 72.01; H, 11.82; N, 3.65; O, 12.51. Found: C, 72.1938; H, 11.796; N, 3.643.
13. (a) Magrioti, V.; Hadjipavlou-Litina, D.; Constantinou-Kokotou, V. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 375. (b) Niiro, H.; Azuma, H.; Tanago, S.; Matsumura, K.; Shikata, K.; Tachibana, T.; Ogino, K. *Bioorg. Med. Chem.* **2004**, *12*, 45.
14. (a) Sisido, K.; Hirowatari, N.; Tamura, H.; Kobata, H.; Takagisi, H.; Isida, T. *J. Org. Chem.* **1970**, *35*, 350. (b) Imashiro, R.; Sakurai, O.; Yamashita, T.; Horikawa, H. *Tetrahedron* **1998**, *54*, 10657.
15. **10**: ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3H, J = 7.0 Hz), 1.20-1.57 (m, 27H), 1.42 (s, 9H), 1.75-1.85 (m, 1H), 2.32 (br, 1H), 3.29 (br, 1H), 3.55-3.78 (m, 3H), 5.20 (br, 1H); Anal. calcd for $C_{23}H_{47}NO_4$: C, 68.78; H, 11.80; N, 3.49; O, 15.93. Found: C, 68.64; H, 11.78; N, 3.48.